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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,022	05/04/2001	Joseph D. Gold	091/005P	7806

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,022	GOLD ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 6/13/06, have been entered. Claims 1-3, 6, 8, 9, 13, 15-36 are cancelled; claims 37 and 38 are newly added, pending and under current examination.

Double Patenting

The prior rejection of claims 1-3, 6, 8, 9, 13, 15-36 as being provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9, 15, 17, 19 of copending Application No. 11/010,140 is withdrawn, because the '140 claims recite the production of differentiated cells, whereas the instant claims are directed to a cell population of undifferentiated hES cells.

The prior rejection of claims 1-3, 6, 8, 9, 16-19 as being provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 10 of copending Application No. 10/141,220 is withdrawn in view of the abandonment of the '220 application.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-3, 6, 8, 9, 13, 15-36 under 35 U.S.C. 112, first paragraph, for enablement, is withdrawn. Applicants' have now amended the claims such that the hES cells are maintained in a culture environment that contains an extracellular matrix and fibroblast-conditioned medium. Claims that are directed to producing specific cell types have now been cancelled, rendering those rejections moot. Applicants' arguments with regard to utilizing promoters

that are expressed in both undifferentiated and differentiated cells are found to be persuasive.

Claim Rejections - 35 USC § 112

The prior rejection of claims 17-21 under 35 U.S.C. 112, second paragraph, is rendered moot in view of Applicants' cancellation of the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 34, 35 and 36 under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* when taken with Bodnar *et al.* in further view of Gerson *et al.* is rendered moot in view of Applicants' cancellation of the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* when taken with Bodnar *et al.* and further in view of Capecchi *et al.* All references cited in the prior Office action, mailed 2/13/06)

The claim is directed to a cell population comprising undifferentiated hES cells essentially free of feeder cells, cultured on an extracellular matrix in a medium conditioned by fibroblast feeder cells, wherein the population comprises cells stably transfected so as to express a protein from a heterologous polynucleotide in which an encoding region for the expressed protein is operably linked to a promoter that promotes transcription of the encoding region while the hES cells are undifferentiated and wherein at least 90% of the undifferentiated hES cells have been stably transfected.

Reubinoff *et al.* teach human embryonic stem cells. They teach that cells are capable of differentiate spontaneous *in* vitro, and the cells stained positively for antibodies against neurofilament proteins and neural cell adhesion molecule (col. 21, lines 49-52) and, when injected into SCID mice, the tumors that formed showed various differentiated tissues, including primitive neuroectoderm and ganglionic structures (col. 22, lines 10-13 and Figure 6). They teach that the stem cells can identified by cell markers or by measuring the gene expression of genes specific to ES cells (such as Oct-4), or to particular cell lineages (col. 11, lines 62-66). They teach that cells can be sorted by using lineage-specific markers, including the use of FACS to isolate cells of interest (col. 6, lines 61-64, col. 14, lines 31-40). They teach that human ES cells can be modified at any stage of isolation, and can be modified by introduction of vectors expression a selectable marker that is under control of a stem cell-specific promoter, such as OCT-4. They teach that the differentiated products of the stem cells can produce gene products that are inhibitory to stem cell

survival, and this system can be used to select for undifferentiated cells (col. 12, lines 8-22).

Reubinoff *et al.* do not teach culturing the hES cells in a culture environment that is essentially free of feeder cells, in the presence of an extracellular matrix, and in a medium conditioned by fibroblast feeder cells. However, prior to the time the claimed invention was made, Bodnar *et al.* teach methods of maintaining primate-derived primordial stem cells in an undifferentiated state by culturing them in a cell culture medium and an extracellular matrix. They teach that a conditioned medium is one that is supplemented with soluble factors derived from feeder cells (page 5, #3.1.2); they teach that feeder cells include mouse embryonic fibroblasts and STO cells (p. 10, lines 1-3) and the extracellular matrix can be derived from these feeder cells (p. 10, line 4). They teach that the primate-derived primordial stem cells can be cultured in feeder-free conditions, using a conditioned medium, and in the presence of a matrix (p. 11, lines 19-24). They further teach that the stem cells can be genetically modified, using methods, such as utilizing a positive-negative selection vector, or any of those known in the art (p. 16, lines 12-21).

Reubinoff *et al.* and Bodnar *et al.* do not teach or suggest that at least 90% of the undifferentiated cells have been genetically altered. Reubinoff *et al.* and Bodnar *et al.* generally contemplate genetically modified embryonic stem cells, and Bodnar *et al.* particularly contemplate using a positive-negative selection vector, as described in Capecchi *et al.* (see p. 16, lines 15). Capecchi *et al.* teach a positive-negative selector vector to modify a target DNA sequence by homologous recombination. Particularly, the vector contains both a positive and negative selection marker in order to identify cells that have been transfected with the construct. In particular, they teach the positive selection comprises contacting cells infected with these vectors, and selecting for cells that do not contain the selection marker. They also teach that negative selection comprises contacting the cells with a particular agent, and cells that are transfected with the vector are killed. See col.

7, lines 29-45. They particularly teach selectable markers that can be used, including drug resistance genes (for example *Neomycin*), See Table I.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to modify the teachings of Reubinoff *et al.* and Bodnar *et al.* one of skill in the art to modify the culture conditions, as taught by Reubinoff *et al.* to conditions which include an extracellular matrix and fibroblast-conditioned medium, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make these modifications in order to reduce potential contamination from any viruses that might be present in the mouse feeder cells, and optimize culture conditions, and as Bodnar states, "[C]urrent methods of culturing primate-derived primordial stem cells require a feeder layer that complicates and slows the process of cell cultivation." Furthermore, one of skill in the art would have been motivated to produce cells that are at least 90% transfected (by positive selection), to produce ES cells that have a drug resistance gene (such as *neomycin*), to select for cells that are transfected (by positive selection), and expression of this positive selection marker supports the growth of the hES cells, in the presence of the selection agent, as taught by Capecchi *et al.*, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification, as Bodnar *et al.* contemplate utilizing Capecchi's methods, and further, teach that utilizing these vectors would provide for an efficient methodology to modify and select for transfected ES cells (see col. 15-16, bridging ¶).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* when taken with Bodnar *et al.* and further in view of Capecchi *et al.*

as applied to claim 37 above, and further in view of Yu *et al.* (**Genesis**, 26: 5-8, January 2000).

Reubinoff *et al.*, Bodnar *et al.* and Capecchi *et al.* are described above. Although they teach using a positive/negative selection system, they collectively do not teach using a promoter such as EF1a or the PGK-promoter. However, prior to the time of filing, Yu *et al.* teach using a positive/negative selection system, wherein the selection cassette encodes a fusion protein with hygromycin-resistance and thymidine kinase activity under control of the CMV promoter, and another negative selection cassette which is under control of the PGK promoter in ES cells. They teach that using this second negative selection cassette, the recombination efficiency within the targeted locus was increased 75-fold. See Abstract.

Accordingly, given the combined teachings, it would have been obvious, for one of ordinary skill in the art, to modify the teachings of Reubinoff, Bodnar and Capecchi, to utilize a selection system that included a cassette under control of the PGK promoter, as taught by Yu *et al.,* with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification, as Yu *et al.* teach the importance of thorough screening of ES cell clones for recombination events and state that the PGK-construct allowed for, "enrichment for correctly targeted ES cell clones." See page 5, 2nd column, 1st ¶, and because Yu *et al.* clearly show that using this construct provides an improved recombination efficiency.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thaian Ton

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